SECTION V

AUTISM SPECTRUM DISORDERS

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Autism spectrum disorders (ASD) are highly heterogeneous conditions that are diagnosed using only behavioral criteria due to a lack of concrete biological markers. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defines ASD as a disorder characterized by deficits in verbal and nonverbal communication, stereotyped behaviors and interests, and impaired social interactions [1–3]. ASD encompasses a wide range of phenotypic severities and comorbidities (reviewed in [4]). ASD likely encompasses several disorders with distinct etiologies and pathologies that converge on a common set of behavioral diagnostic criteria. Although autism risk has strong heritability, no single locus alone appears to be sufficient to account for the full clinical phenotype [5–7]. Results from over 12 genomewide autism screens indicate that potential susceptibility genes are spread across the entire genome [8, 9]. Recently, several very rare genetic mutations [7, 10–12], single nucleotide polymorphisms (SNPs) [13], *de novo* copy number variations [14], and epigenetic factors that influence DNA methylation [15, 16] were shown to contribute complexity in the transmission of autism risk. Yet genetics alone cannot account for the majority of autism cases currently being diagnosed. There is lack of full concordance between monozygotic twins, with some estimate ranging as low as 60% [17], and the prevalence of ASD among siblings has been reported as high as 14% [18]. Interactions among multiple genes are likely to contribute to various types of autism, and heritable epigenetic factors and/or nonheritable environmental exposures are likely to significantly contribute to susceptibility and variable expression of autism and autism-related traits. Therefore, it is likely that constellations of epigenetic and environmental factors are contributing to the increasing prevalence of ASD, a rise that cannot be fully accounted for by changes in diagnostic criteria [19]. A major challenge in the field is to identify environmental factors of relevance to autism. Current efforts to identify clinical endophenotypes within the autism spectrum are therefore likely to help our understanding of the constellations of genes that confer differential sensitivity to distinct environmental exposures during gestational and neonatal development. Such approaches will likely prove useful

in defining subgroups of children that differ in susceptibility to specific types of environmental exposures that promote autism risk, severity, and responsiveness to clinical and behavioral interventions.

In this section of the book, we review our current understanding of the neurobiological basis of ASD and how exposures to persistent organic pollutants such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and heavy metals may converge on the same signaling pathways already impaired in children at risk for ASD (Chapter 21). Especially relevant are convergent mechanisms that disrupt the balance of excitation and inhibition within neuronal circuits [20]. Chapter 22 focuses on oxidative defense mechanisms and how they may be impaired in ASD to produce oxidative stress and enhanced susceptibility to reactive oxygen species and inflammation. Several of the gene variants associated with ASD influence proteins that are not only expressed in brain but are also expressed within the immune system. Chapter 23 reviews evidence for a role of neuroinflammation in ASD, whereas Chapter 24 provides new evidence for differential responses of peripheral mononuclear blood cells to antigens and PBDEs. Chapter 25 proposes development of novel methodology to better study gene-environment interactions between benzo(a)pyrene (B(a)P), the prototypical polycyclic aromatic hydrocarbon (PAH) environmental toxicant, and MET receptor tyrosine kinase, an autism candidate gene [13].

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